

Case report

Melkersson-Rosenthal syndrome with coeliac and allergic diseases

Joana Albuquerque Martins,^{1,2} António Azenha,^{1,2} Rui Almeida,³
João Páscoa Pinheiro^{1,2}

¹Physical and Rehabilitation Medicine Department, Centro Hospitalar e Universitário de Coimbra EPE, Coimbra, Portugal
²Faculty of Medicine, University of Coimbra, Coimbra, Portugal
³Department of Pathology, Centro Hospitalar e Universitário de Coimbra EPE, Coimbra, Portugal

Correspondence to

Dr Joana Albuquerque Martins,
joanamrmartins@hotmail.com

JAM and AA contributed equally.

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SUMMARY

A 45-year-old man presented with a 10-year history of relapsing oedema of the lips. Moreover, he exhibited recurrent facial nerve palsy since the age of 10 years, coeliac disease since the age of 12 years, atopic eczema, allergic rhinitis and asthma. Physical examination revealed lip swelling and lingua plicata. Thus, he presented the classic triad of Melkersson-Rosenthal syndrome which includes recurrent orofacial oedema, facial nerve palsy and fissured tongue. A lip biopsy confirmed our clinical diagnosis. This case is particularly rare, as the classic triad is seen only in a minority of the cases. Moreover, allergic and coeliac diseases were observed concomitantly. This paper illustrates a potential pathophysiological interconnection between these pathologies in which interferon gamma could play a key role. To our knowledge, this is the first case report in which Melkersson-Rosenthal syndrome has been observed concurrently with coeliac disease.

BACKGROUND

Melkersson-Rosenthal syndrome is a rare granulomatous disease that classically consists of a triad of recurrent orofacial oedema, facial nerve palsy and fissured tongue.¹⁻³ It usually presents in a monosymptomatic or oligosymptomatic form and oedema of the lips is the most common monosymptomatic presentation, also termed Meischer's syndrome or cheilitis granulomatosa. Several comorbidities have been reported in association with this disease. However, the underlying aetiology and pathogenesis remain unknown.^{1,4}

In this paper, we present a rare case of Melkersson-Rosenthal syndrome associated with allergic and coeliac diseases.

CASE PRESENTATION

A 45-year-old man presented with a 10-year history of relapsing and progressively persistent oedema of the lips. Moreover, the patient was also affected by recurrent alternate facial nerve palsy since the age of 10 years, coeliac disease since the age of 12 years (for which he was under a gluten-free diet), atopic eczema, allergic rhinitis and asthma. Family history was irrelevant.

Physical examination revealed swelling of the lips (figure 1A), more notorious on the lower lip (figure 1B), a herpetic lesion on the left vermilion border of the upper lip and deep fissure grooves on the dorsal surface of the tongue consistent with

lingua plicata. A mild sequelar bilateral facial palsy was also noted.

Thus, the patient demonstrated the classical Melkersson-Rosenthal syndrome triad, which is seen only in a minority of the cases.

INVESTIGATIONS

A lip biopsy was performed, and the histopathology revealed perivascular epithelioid granulomas with Langhans multinucleated giant cells without necrosis (figure 1C) which was compatible with our clinical diagnosis.

Since this syndrome is of unknown aetiology and can be associated with several pathologies, a complementary investigation was carried out. The results of basic laboratory tests, including complete blood count, liver and kidney function tests, serum calcium, glucose level, C reactive protein and erythrocyte sedimentation rate, were normal. Angiotensin-converting enzyme, β 2-microglobulin, free thyroxine, thyroid-stimulating hormone and complement (C3, C4, C1q) levels were within normal range. The levels of IgA, IgG, IgM antibodies were within the range. Also, antineutrophil cytoplasmic antibodies, anti-DNA, anti-JO1, anti-centromere, anti-Scl70, anti-SSA, anti-SSB were negative or within normal range. Serologic test for herpes simplex virus (HSV) revealed previous HSV-1 infection. Epicutaneous skin tests showed nickel allergy. Chest X-ray was normal and colonoscopy revealed ileal erythema, but its biopsy did not confirm inflammatory changes.

TREATMENT

Prednisolone was administered orally at 1 mg/kg/day, with gradual tapering off, in combination with valacyclovir for a month. He also performed a rehabilitation programme with different physical modalities. This combination treatment resulted in gradual and almost complete resolution of the swelling.

OUTCOME AND FOLLOW-UP

The patient maintained follow-up at our department. No episode of facial paralysis or orofacial oedema has been observed in the last year.

DISCUSSION

The Melkersson-Rosenthal syndrome was first described in 1928 as a triad of recurrent orofacial oedema, recurrent facial nerve palsy and fissured



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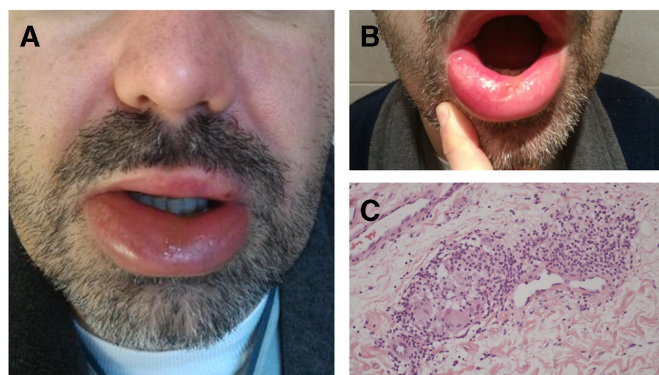


Figure 1 Photographs showing swollen of the lips (A), more notorious on the lower lip (B) and histological findings of the lip biopsy (C). H&E 200× magnification.

tongue and has an estimated incidence of 0.08%.¹⁵ The complete triad occurs only in a minority of cases, ranging from 8% to 18%, with the monosymptomatic and oligosymptomatic forms being the most frequent presentations.^{4 6} Other signs and symptoms that have been associated with this syndrome are fever, unilateral hyperacusis, tinnitus, neuralgia of tragus and ear channel, vasomotoric hemicrania, taste disturbances, disorders of lacrimal or salivary secretion, trigeminal neuralgia, paraesthesia, ocular nerve palsy, blepharospasm, keratitis, uveitis, psychotic episodes and meningeal signs.^{1 6 7}

Regarding the histopathological findings, the microscopy of the labial biopsy in Melkersson-Rosenthal syndrome typically reveals dilation of lymphatic vessels with aggregates of lymphocytes, histiocytes and plasmacytes in an initial stage of the disease. At a later stage, the classical histopathological findings of non-caseous granulomatous inflammation can be observed with Langhans multinucleated cells, which was the case of the patient presented. This granulomatous inflammation, however, is not observed in more than half of the cases, and its absence should not rule out the diagnosis which is essentially clinical.⁸

The treatment of this syndrome remains empirical and, in many cases, unsuccessful. Systemic corticosteroids are the least invasive and most frequently used treatment and have proved to be effective although only temporarily in some cases.¹ Some antibiotics, namely roxithromycin, minocycline and dapsone, have also been used in the treatment of this syndrome with modest effect.^{9–11} In some studies, regarding surgical treatment, facial nerve decompression has been shown to be effective in the prevention of future episodes of facial palsy in Melkersson-Rosenthal syndrome.^{12 13} Concerning plastic surgery, cheiloplasty can be considered in the case of permanent fibrotic deforming lesions.^{1 14 15} Finally, some authors have recently reported success with adalimumab^{3 16–18} and infliximab,^{19–21} both antitumour necrosis factor alpha (anti-TNF- α) agents. In our patient, an almost complete resolution of the swelling was observed with oral administration of prednisolone.

Although the aetiology and pathophysiology of Melkersson-Rosenthal syndrome remain unknown, several theories have been hypothesised as follows. The genetic predisposition is one of the most suggested aetiologies, and some authors even propose an autosomal dominant transmission with variable penetrance, in which the gene involved would be located at locus 11 of chromosome 9 (9p11).^{22 23} The allergic origin has also been suggested, as the prevalence of atopy in patients with Melkersson-Rosenthal syndrome is about 14%–60% and an association with hypersensitivity reactions to some food additives and

cobalt has also been reported.^{4 24} An infectious aetiology has also been proposed, and an association with HSV infection, toxoplasmosis and some spirochetes has been found.^{25 26} Autoimmunity has also been suggested as an aetiological factor, as there is an association of this syndrome with several autoimmune diseases such as Crohn's disease and sarcoidosis.^{26 27} Melkersson-Rosenthal syndrome has also been reported in association with mixed connective tissue disease, discoid lupus erythematosus and Hashimoto's thyroiditis.^{2 28–31}

In the presented case, the coexistence of Melkersson-Rosenthal syndrome with allergic disease and coeliac disease was observed.

Coeliac disease is an autoimmune disease that occurs in patients with genetic predisposition and exposed to gluten. The immune response involves both the adaptive and the innate immune system. The innate immune response occurs in the intestinal epithelium and involves the production of IL-15 by enterocytes, macrophages and dendritic cells. This results in the differentiation of intraepithelial lymphocytes into cytotoxic lymphocytes, leading to the damage of the intestinal mucosa by the released inflammatory mediators, mainly interferon gamma (IFN- γ), TNF- α and lymphotoxin- α . In turn, the adaptive immune response occurs on the lamina propria, after fragments of gliadin cross the epithelial barrier of the mucosa, where antigen-presenting cells, such as macrophages and dendritic cells, expressing HLA II DQ2 and/or DQ8 molecules in their surface, uptake and display gliadin peptides. These cells then interact with Th1 lymphocytes, which produce inflammatory cytokines such as IFN- γ . Thus, there is a predominance of Th1 pattern of cytokine production produced by T lymphocytes, as is generally the case in autoimmune diseases.^{32–34}

In contrast, allergic disease is classically characterised by a Th2 immune deviation, with a high production of cytokines such as IL-4. However, some studies demonstrated a high production of IFN- γ in patients with atopy, which was concluded to be due to its production by T cytotoxic lymphocytes and not by T helper lymphocytes.^{35 36}

Considering that Melkersson-Rosenthal syndrome is a chronic granulomatous disease, Th1 lymphocytes will play a central role, since they produce IFN- γ that activate macrophages to produce cytokines such as TNF- α , which is essential in the formation and organisation of granulomas.³⁷ Thus, we hypothesise that in this case the coexistence between Melkersson-Rosenthal syndrome, coeliac disease and allergic disease is not a mere coincidence and may have a common pathophysiological basis, in which IFN- γ may have a key role.

In this paper, we report a case of Melkersson-Rosenthal syndrome with a very unusual presentation and illustrate the

Learning points

- ▶ Melkersson-Rosenthal syndrome classically consists of a triad of recurrent orofacial oedema, facial nerve palsy and fissured tongue, but it usually presents in a monosymptomatic or oligosymptomatic form.
- ▶ Although the underlying aetiology is still unknown, several comorbidities such as Crohn's disease have been reported with this syndrome and must be excluded.
- ▶ The coexistence of this syndrome with allergic and coeliac diseases may not be a coincidence but instead be related to a common pathophysiological basis, in which interferon gamma could have a key role.

potential interconnection between this syndrome and the allergic and coeliac diseases. To the best of our knowledge, this is the first case in which Melkersson-Rosenthal syndrome has been observed concurrently with coeliac disease.

Contributors JAM and AA performed the clinical study, diagnosis of the patient and drafted the manuscript. RA performed anatomopathological analysis and was involved in clinical data acquisition. JPP revised the manuscript. All authors read and approved the final manuscript.

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